Drug points

Vaccination reactions and thiomersal

Drs NEIL H COX, W NEIL MORLEY (Department of Dermatology, Royal Hospital for Sick Children, Glasgow), and ANGELA FORSYTHE (Contact Dermatitis Investigation Unit, Belvidere Hospital, Glasgow) write: We were interested to read the comments by Dr Norman Begg (1 November, p 1155) on local reactions to triple vaccine. We describe a patient who illustrates a further possible cause for such reactions.

This girl had had a history of atopic dermatitis since the age of 4 months and of asthma since the age of 2 years. Her sister had atopic dermatitis. The patient developed an abscess at the site of her first triple vaccine (DPT) injection, and two further DPT vaccinations in the following 18 months caused severe local reactions and exacerbation of dermatitis at antecubital and popliteal fossae, wrists, and ankles. At the age of 5 a booster vaccination to diphtheria alone also caused a similar reaction. Patch testing was performed when she was 5½ because of possible exacerbations of dermatitis related to footwear. The only positive reaction was to thiomersal (1+ at 48 and 96 hours), which is used as a preservative in vaccines. Negative results were obtained to the European standard battery, rubber, chemicals, footwear battery, and other organomercurials (which may be used in leather processing). This girl's adverse reactions to DPT immunisations were probably due to the pertussis component but this would not explain the recent reaction to diphtheria vaccine alone. Local reactions to diphtheria vaccine are rare in children under 2 years, as is allergic contact dermatitis, and a clinically relevant positive patch test result must be taken seriously. We therefore believe that the likely cause of the recent vaccination reaction in this patient was her allergy to thiomersal, even if the earlier reactions to DPT vaccinations were due to the pertussis component.

Thiomersal 0·01% (thimerosal, merthiolate, sodium ethylmercurithiosalicylate) is used as a preservative in Trivax DPT vaccine (Wellcome) and is present in all brands of diphtheria, pertussis, and tetanus vaccines available in the UK. In the past five years 56 patients referred to the contact dermatitis investigation unit have had positive patch test reactions to thiomersal (about 1% of patients). As in most series, many of these are not clinically relevant (in adults local reactions to contact lens soaking solutions, eyedrops, or nasal drops are the usual presentation of allergic contact dermatitis due to thiomersal). It is possible that many positive patch test reactions to thiomersal may be due to sensitisation at the time of vaccinations.

Make a comparison possible: ceruletide

Dr PAUL BINGHAM (Nazareth Hospital, Nazareth, Israel) writes: I was pleased that Drs Raffaele Tritapepe and Carlodi Padova (25 October, p 1102) shared their experience with irrigation plus ceruletide in the treatment of retained biliary stones, but what a pity they did not make their data comparable with that in the paper they were commenting on. In that paper the number of patients cured by one treatment was stated (6 September, p 595). Drs Tritapepe and Padova give only details of stones dissolved, and it is mathematically possible that they also had only an initial 30% cure rate. Surely it is vital that when original data are given in comment on a paper it is presented in a way that it can be compared with that paper, especially if the details are readily available. This is another issue touching the quality of research.[1]

1 Dickersin K, Hewitt P. Look before you quote. *Br Med J* 1986;293:1000-2.

Desensitising vaccines

Dr J H TOOGOOD (Allergy Clinic, Victoria Hospital, London, Ontario N6A 4G5) writes: The CSM Update on densensitising vaccines points out the risk of fatal anaphylaxis as a complication of desensitisation therapy (11 October, p 948). The data presented suggest that the incidence of these deaths in the United Kingdom might have been increasing in recent years. Factors other than the antigen per se may contribute to this problem. For example, β adrenergic blockade increases the severity of and mortality from experimental anaphylaxis[1-3] and in clinical practice exceptionally severe or fatal anaphylactic reactions have been triggered by desensitisation injections given to patients receiving β blocker therapy for an unrelated condition.[4-7]

Pharmacological β blockade interferes with the normal "shut off" mechanisms that modulate the synthesis and release of anaphylaxis mediators,[2,8,9] and a relatively trivial antigenic challenge may trigger a massive and persisting discharge of mediators. Furthermore, the β blockade abrogates the effectiveness of the adrenergic drugs on which one normally relies to rapidly control the anaphylaxis.[2] This association between β blocker treatment and augmented anaphylactic sensitivity is being increasingly recognised in American and Canadian reports. It would be worth re-examining the data in the CSM Update to determine whether any of the 26 patients who died from anaphylaxis were receiving concomitant β blocker therapy. The temporal association between the increase in the number of fatal reactions to desensitisation reported in the United Kingdom and the increasingly widespread use of β blocker drugs might be more than coincidental.

1 Nisam MR, Zbinden Z, Chesrown S, Barnett D, and Gold WM. Distribution and pharmacological release of histamine in canine lung in vivo. *J Appl Physiol* 1978;44:455-63.
2 Toogood JH. Beta-blocker therapy and the risk of anaphylaxis. *Can Med Assoc J* (in press).
3 Matsumura Y, Tan EM and Vaughan JH. Histamine hypersensitivity in mice induced by bordetella pertussis or pharmacologic beta adrenergic blockade. *J Allergy Clin Immunol* 1976;58:395-404.
4 Frankish C, McCourtie D, Toogood JH. Anaphylactic death in patient on beta blockers. *Clin Invest Med* 1985;8:A42.
5 Jacobs RL, Rake GW Jr, Fournier DC, Chilton RJ, Culver WG, Beckmann CH. Potentiated anaphylaxis in patients with drug-induced beta-adrenergic blockade. *J Allergy Clin Immunol* 1981;68:125-7.
6 Newman BR, Schultz LK. Epinephrine-resistant anaphylaxis in a patient taking propranolol hydrochloride. *Ann Allergy* 1981; 47:35-7.
7 Bickell WM, Dice WH. Military antishock trousers in a patient with adrenergic-resistant anaphylaxis. *Ann Emerg Med* 1984; 13:189-90.
8 Lemanske RF, Casale TB, Kaliner M. The autonomic nervous system in allergic disease. In: Kaplan AP, ed. *Allergy*. New York: Churchill Livingstone, 1985:199-213.
9 Assem ASK. Adrenergic mechanisms and immediate-type allergy. *Clin Allergy* 1974;4:185-94.

Prescribing in pregnancy

Dr T PULLAR (Department of Medicine, General Infirmary, Leeds LS1 3EX) writes: Dr Peter Rubins (29 November, p 1415) classified non-steroidal anti-inflammatory drugs in his category of drugs which are present in breast milk but reach the baby in insignificant dose. There has been one report of convulsions in a baby whose mother was taking indomethacin while breast feeding and it was argued that this reaction may have been related to reduced glucuronidation in neonates resulting in accumulation.[1] Needs and Brooks therefore recommend avoidance of indoleacetic acids during lactation, and in view of the plethora of alternative agents this is reasonable advice.[2]

1 Eeg-Olofsson O, Malmros I, Elwin C-E, Steen B. Convulsions in a breast-fed infant after maternal indomethacin. *Lancet* 1978; ii:215.
2 Needs CJ, Brooks PM. Antirheumatic medication during lactation. *Br J Rheumatol* 1985;24:291-8.

Antitetanus vaccination

Drs S C ROBERTS and W M SHEPHERD (Department of Clinical Immunology and Chemotherapy, Wellcome Research Laboratories, Beckenham, Kent BR3 3BS) write: We would like to comment on two recent Any Question replies about antitetanus vaccination (18 October, p 1020; 1 November, p 1155). Tetanus toxoid is a very effective immunogen but the duration of protection depends on the antigen content and formulation, on the number and scheduling of doses, and on individual variation both in the initial immune response and in the persistence of circulating tetanus antibodies. Computation of antitoxin regression rates indicates that in eight years antitoxin titres below the accepted minimum protective level (0·01U/ml) would be predicted in 0·1% of a population receiving five doses of standard vaccine in a routine course.[1] As tetanus is a non-transmissible disease for which there is no herd immunity, the desired goal should be protective antitoxin concentrations in all individuals. Thus it is generally recommended that subjects be boosted at intervals of no longer than 10 years.

The second point with which we would take issue concerns the use of skin tests. Dr Norman Begg (p 1155) suggests that these might be used to investi gate hyperimmunisation against tetanus; however, positive cutaneous reactions can occur in under-immunised subjects as well as in those who have shown no clinical reactivity to prior tetanus immunisations.[2] Skin tests in the individual case are therefore of little value in determining immunisation state or in predicting future reactivity to tetanus vaccination. Apparent reactors to tetanus vaccination should be given 0·1 ml doses of fluid tetanus toxoid (or tetanus/diphtheria toxoid for infants). This reduced dose administered intradermally is less reactive and is sufficient to promote a booster response.[3] (Fluid toxoid is ineffective, however, when administered with tetanus immunoglobulin, and adsorbed vaccine should accompany passive prophylaxis. Adsorbed vaccines should never be administered intradermally.)

1 Peebles TC, Levine L, Eldred MC, Edsall G. Tetanus-toxoid emergency boosters—a reappraisal. *N Engl J Med* 1969;280: 57581.
2 White WG, Barnes GM, Barker E, *et al.* Reactions to tetanus toxoid. *J Hyg (Camb)* 1973;71:283-97.
3 Ruegsegger JM. Further observations on the prevalence of tetanus antitoxin. *Arch Intern Med* 1960;106:410-6.

Bilateral scopolamine mydriasis in a traveller

Drs GABRIELLA MARIA MARCON and FERDINANDO SCHIAVO (Ospedale Civile di Udine, 15-Udine, Italy) write: Scopolamine, an anticholinergic agent with an antiemetic action used to combat motion sickness, has been available since 1981 in the form of slow release adhesive for application behind the ears. Applied on one side two hours before travelling the strips ensure transdermal absorption of the drug for up to 72 hours,[1] which should avert its side effects, provided that the instructions are complied with strictly. It is important not to touch the adhesive surface of the strips, to apply the latter with dry hands, and to wash the hands well after applying or removing them. Moreover, if protection is needed for more than 72 hours a second strip may be applied in a different area behind the ears.

A 46 year old woman with a history of migraine and mild hypertension was admitted in August 1985 because of bilateral amblyopia, nausea, vomiting, subjective vertigo, dryness of the mouth, and intense dragging headache refractory to drugs. The symptom complex had appeared four days before, during a coach trip to France, and had later worsened. On admission the patient presented bilateral mydriasis unreactive to light, accommodation, or convergence and mild drowsiness, which, combined with the intense headache, made proper history taking impossible. Only in conversation with the husband some hours later did it emerge that the patient had used the scopolamine strips to prevent motion sickness, two every 72 hours, had repeatedly "rubbed" them to heighten the effect, and had not kept to the instructions. The clinical signs and symptoms cleared 36 hours after admission on rehydration therapy alone.

Only one case of mydriasis due to transdermal scopolamine has been reported to date and that was unilateral, in a 9 year old girl who had applied the strips on one side only, that of the subsequent mydriasis.[2] We attribute the side effects in our case to the transdermal mode of application rather than to direct penetration of the nervous structures by the drug.

1 Price NM, Schmitt LG, McGuire J, Shaw JE, Trobough G. Transdermal scopolamine in the prevention of motion sickness at sea. *Clin Pharmacol Ther* 1981;29:414-9.
2 Lebuisson DA, Risvegliato M. La mydriase unilatérale du voyageur. *La Presse Médicale* 1983;12:2214.